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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/621,268	07/21/00	GILLES S	LEX-007

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HM12/0410

EXAMINER	
PRASAD,S	
ART UNIT	PAPER NUMBER
1646	4

DATE MAILED: 04/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Offic Action Summary	Application No.	Applicant(s)	
	09/621,268	Gilles et al.	
	Examiner	Art Unit	
	Sarada C Prasad	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26,44 and 45* is/are pending in the application.

4a) Of the above claim(s) *27-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26,44 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

Detailed Action

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C.121.

Group I (1-26, 44-45) is drawn to a method of enhancing the immunogenicity of a pre-selected antigen in a mammal, comprising administering to the mammal a fusion protein comprising an immunoglobulin heavy chain constant region linked by polypeptide bond to the pre-selected antigen to elicit a stronger immune response, classified in class subclass;

Group II (27-43) drawn to a method of enhancing the immunogenicity of a pre-selected antigen in a mammal, comprising administering to the mammal a nucleic acid sequence encoding a fusion protein comprising an immunoglobulin heavy chain constant region linked to the pre-selected antigen, whereupon expression of the nucleic acid sequence in the mammal results the production of the fusion protein which then elicits a stronger immune response, classified in class subclass.

These two inventions are distinct because they are materially different from each other and require different process steps. For example, the two inventions in Groups I and II are directed to immunization procedures involving different criteria for immunogen preparation followed by distinct methods. For example, invention of Group I requires polypeptides comprising fusion proteins, adjuvant, and the pre-selected antigen, while Group II requires in addition to fusion protein, and adjuvant, the pre-selected antigen in the form of nucleic acid fusion protein with additional control for its expression *in vivo* in the immunized animal. Hence, each invention is not necessary for the practice of the other.

These inventions are also distinct because of their different classification and a search for invention I would not reveal art for invention II. Therefore, restriction for examination purposes as indicated is proper.

During a telephone conversation with Attorney Stephen Brodowsky on 3/13/01 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-26, 44-45. Affirmation of this election must be made by applicant in replying to this Office action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Therefore, claims 1-26, 44,45 are under consideration by the Examiner. Claims 27-43 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 11-13, 24-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for IL-2, GMCSF, IL-4R, FLT-3L as adjuvants in a method of enhancing the immunogenicity of a pre-selected antigen, does not reasonably provide

enablement for 'all other' cytokines as adjuvants in a method of enhancing the immunogenicity of a pre-selected antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/practice the invention commensurate in scope with these claims.

Claims 11 and 24 are overly broad in reciting 'the method of ....., wherein the adjuvant protein is a cytokine' and 'the composition of claim 15, wherein the adjuvant.....is a cytokine' respectively. The instant claims can be read to imply any cytokine as being capable of providing the adjuvant function. However, as disclosed in the instant specification there are certain preferred cytokines that perform the adjuvant function (page 6, paragraph 1, lines 7-end), for example: interferon-γ, interleukin-2, intereleukin-4, intereleukin-12, intereleukin-18, tumor necrosis factor, granulocyte macrophage colony stimulating factor, and an extracellular domain of a protein that usually is particularly membrane-bound. Even though this is a long list of cytokines, usage of a general term such as 'cytokine' in the instant claims can include innumerable number of proteins that are classified as cytokines for various reasons. Furthermore, the enablement of the instant invention requires preparation of fusion proteins of various adjuvants (cytokines), constant region of the Ig chain as the locator protein, and a variety of pre-selected antigens in various combinations either singly or together. The Applicants have provided these three components in several mix and match combinations either in the form of fusion proteins or admixtures that are not in covalent linkage. However, it requires undue experimentation to test all of the possible combinations other than what are shown as working examples in the specification with the amount of guidance provided in the specification. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation

is necessary, is it undue (In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404). Considering the breadth of claims 11 and 24, guidance provided in the specification, working examples, the amount of experimentation required is undue to practice the invention as claimed.

Claims 12-13, and 25 are rejected insofar as they depend on claims 11, and 24.

Claim Rejections - 35 USC § 112-second para

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 44-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3a. Claims 44-45 recite 'fusion proteins comprising localizing protein'. It is unclear as to what exactly is meant by the term localizing protein in these instant claims. This rejection can be obviated by defining clearly what the localizing protein in each case is.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims1-26, 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harvill et al. (1996) in view of U.S. Patent No. 5,349,053.

Harvill et al demonstrated constructuion of an IgG3-IL-2 fusion protein that combines the Ag-binding and effector functions of IgG3 with immune stimulatory activities of IL-2 (page 3166, column 2, lines 1-3). Harvill et al also pointed out that the large increase in Ab production in mice immunized with anti-DNS-IgG3-IL-2 bound Ag suggests that this approach to vaccination may be successful with a wide variety of antigens (4th para, page 3169, lines 1-4). Disclosure of Harvill et al. also pointed out that the IgG3 fusion protein was also found to be unique among all the IgGs in having an extended hinge region of 62 amino acids that serves as a spacer separating the Fab from the Fc to which Il-2 is attached.

However, Harvill et al. did not teach how to mix and match (i) the various constant regions of the Ig molecules as localizing proteins for fusion, (ii) cytokines as adjuvants for fusion, in combination with various pre-selected antigens for fusion. Harvill et all also expressly point out the role of the locator molecule in the fusion protein that would assist in colocalizing the antigen fusion protein and the adjuvant fusion protein to same or similar antigen presenting cells. U.S. Patent No.5,349,053 (Landolfi et al) teaches chimeric ligand/immunoglobulin molecules and their uses (title). In particular, the disclosure of Landolfi et al shows chimeric

molecules having a ligand component linked to an immunoglobulin constant region component that can exhibit a high degree of specificity associated with the ligand, yet retain various effector functions characteristic of immunoglobulin heavy chains (abstract, lines 4-7).

Therefore, it would have been obvious to one of skill in the art to combine the teachings of Harvill et al and U.S. Patent No.5,349,053 to achieve the combined benefit of enhancing the immunogenicity of pre-selected antigens by preparing the fusion proteins with various cytokines, variously selected, humanized Ig constant regions, thus rendering obvious the methods recited in claims 1,2, 4-7, 11-13, 15-20, 24-26, and 44-45.

It is well known in the state-of-the-art methods to inject antigen and adjuvant either together or separately one after another (for example, Fc-antigen followed by Fc-adjuvant or Fc-adjuvant followed by Fc-antigen) thereby making claims 2,3 obvious.

U.S. Patent No. 5,349,053 teaches uses of fusion proteins of Ig-constant domains such as CH2, CH3, CH4 which retain various effector functions characteristic of the heavy chains and hence can localize the fusion proteins to cells that have receptors for Ig constant regions. Hence claims 5,6,7 are obvious.

It is the state-of-the-art knowledge to inject humanized vaccine antigens and hence selection of Ig heavy chain region specific to humans in making the fusion proteins, therefore claims 8, 9 are obvious.

The motivation for using prostate specific antigen, or cytokine or viral protein, and a tumor specific protein is provided by the need to obtain antibodies for use in therapy of cancer of these various types thereby making claims 10 and 22 obvious.

Furthermore, selection of cytokines such as IL-12, IL-4, IL-10 as adjuvants instead of Freund's adjuvant or CpG polymers has been in practice thereby rendering claims 11-13, 24-25 obvious. Preparation of distinct fusion proteins with various pre-selected antigens and various cytokine-adjuvant proteins would be advantageous to try various combinations of the different fusion proteins for quantitating the effective enhancement of immunogenicity. Therefore it would have been obvious to prepare different fusion proteins for the antigen and the adjuvant protein rather than a single fusion protein for antigen-adjuvant-Ig constant region, thereby making claims 2, 15, 44 and 45 obvious.

The pharmaceutical composition of claims of 44 and 45 are obvious over claim 12 of U.S. Patent No. 5,349,053 because the patented claim teaches compositions of immunoligands made up of fusion proteins with a suitable carrier. It would be obvious to include two fusion proteins in one composition instead of one fusion protein in one composition because such a composition would include the benefits of both having the antigen and the adjuvant as separate components for testing the mix and match combinations.

5. No claims are allowed.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarada C Prasad whose telephone number is 703-305-1009. The examiner can normally be reached Monday – Friday from 8.00 AM to 4.30 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceedings should be directed to the receptionist whose telephone number is 703-308-0196.

Sarada Prasad, Ph.D.
Examiner Art Unit 1646
April 5th, 2001

Prema Mertz
PREMA MERTZ
PRIMARY EXAMINER